ORGANIC LETTERS

2011
Vol. 13, No. 7
1800–1803

Semicarbazones from *N*-Hydroxyureas and Amines: A Novel Entry in the Reactivity of the Acyl Nitroso Group

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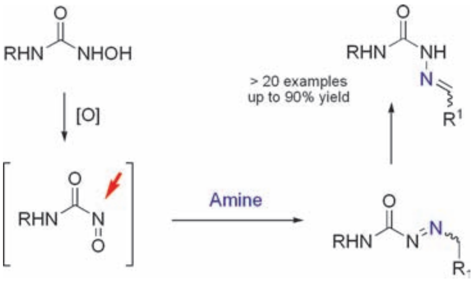
Received February 2, 2011

ABSTRACT



The condensation of carbamoyl nitroso compounds, obtained by oxidation of *N*-hydroxyureas, with amines unexpectedly afforded semicarbazones (aka carbamoyl hydrazones). Although the substitution of the nitrosyl moiety might compete to afford the corresponding urea, an excess of amine led to the semicarbazone as the major product, which is presumably formed via isomerization of an initially generated acyl azo compound.

The discovery of important roles in a number of biological metabolic processes has focused attention on *C*-nitroso compounds in recent decades.[1] These compounds are particularly used as reactive dienophiles in Diels–Alder-type reactions, and the unique properties of this versatile, although elusive, functional group continue to drive the synthesis of nitrogen-containing molecules.[2] Acyl nitroso compounds, which can be considered equivalents of a 1,2-dicarbonyl function, are known to react at the carbonyl site to give amides.[3] However, addition reactions on the labile nitroso moiety have not been described to date.

We report here an unprecedented type of reactivity of carbamoyl nitroso compounds in the presence of amines to give semicarbazones.[4,5] We investigated a possible mechanism that involves an initial condensation between the nitroso group and the amine and we explored the structural features of the key azo-semicarbazone isomerization using computational methods.

In the course of our investigations on the reactivity of carbamoyl nitroso compounds,[6] the formation of two main products was observed when the *N*-hydroxyurea[7] **1** was treated with tetrabutylammonium periodate in the presence of 400 mol % of cyclohexenylethylamine. One of these products was the expected urea **3**, formally obtained by the nitroso group substitution of the carbamoyl nitroso

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(1) (a) Miller, T. W.; Isenberg, J. S.; Roberts, D. D. *Chem. Rev.* **2009**, *109*, 3099. (b) Fukuto, J. M.; Ignarro, L. J. *Acc. Chem. Res.* **1997**, *30*, 149. (c) Averill, B. A. *Chem. Rev.* **1996**, *96*, 2951. (d) Butler, A. R.; Williams, D. L. H. *Chem. Soc. Rev.* **1993**, *22*, 233.

(2) (a) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514. (b) Zuman, P.; Shah, B. *Chem. Rev.* **1994**, *94*, 1621.

(3) Atkinson, R. N.; Storey, B. M.; King, S. B. *Tetrahedron Lett.* **1996**, *37*, 9287.

(4) Semicarbazones and their thio derivatives are often found in biologically relevant molecules. See: (a) Yu, Y.; Kalinowski, D. S.; Kovacevic, Z.; Siafakas, A. R.; Jansson, P. J.; Stefani, C.; Lovejoy, D. B.; Sharpe, P. C.; Bernhardt, P. V.; Richardson, D. R. *J. Med. Chem.* **2009**, *52*, 5271. (b) Christlieb, M.; Dilworth, J. R. *Chem.—Eur. J.* **2006**, *12*, 6194. (c) Lobana, T. S.; Sharma, R.; Bawa, G.; Khanna, S. *Coord. Chem. Rev.* **2009**, *253*, 977. (d) Klayman, D. L.; Bartosevich, J. F.; Griffin, T. S.; Mason, C. J.; Scovill, J. P. *J. Med. Chem.* **1979**, *22*, 855.

(5) Semicarbazones are commonly synthesized by condensation of carbonyl compounds with the corresponding semicarbazide. See: de Oliveira, R. B.; de Souza-Fagundes, E. M.; Soares, R. P. P.; Andrade, A. A.; Krettli, A. U.; Zani, C. L. *Eur. J. Med. Chem.* **2008**, *43*, 1983.

(6) Unpublished results.

(7) For preparation of *N*-hydroxyureas see: Paz, J.; Pérez-Balado, C.; Iglesias, B.; Muñoz, L. *J. Org. Chem.* **2010**, *75*, 8039.

10.1021/ol2003226

Scheme 1. Reactivity of Carbamoyl Nitroso Compounds

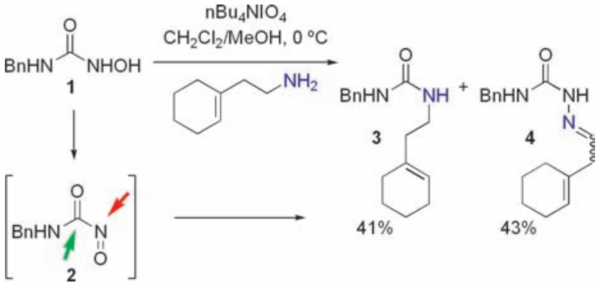
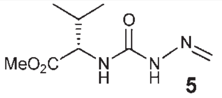
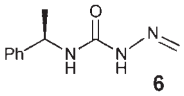
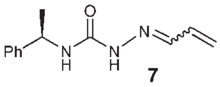
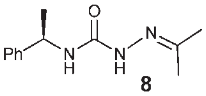
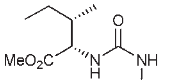
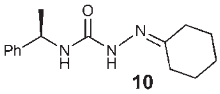
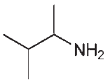
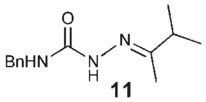
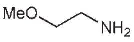
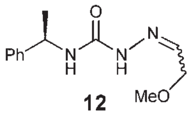
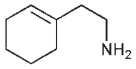
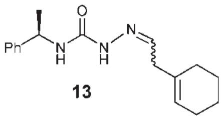
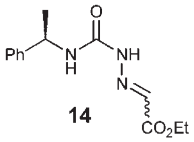
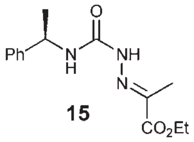
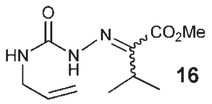
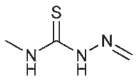


Table 1. Semicarbazones from Alkylamines

entry	amine	semicarbazone	yield
1	$MeNH_2$	 **5**	86%
2	$MeNH_2$	 **6**	91%
3	Allylamine	 **7**	*E*-73% *Z*-16%
4	*i*$PrNH_2$	 **8**	68%
5	*n*$BuNH_2$	 **9**	*E*-62% *Z*-16%
6	Cyclohexylamine	 **10**	72%
7		 **11**	62%
8		 **12**	*E*-59% *Z*-15%
9		 **13**	*E*-54% *Z*-18%
10	GlyOEt	 **14**	62%
11	AlaOEt	 **15**	23%
12	ValOMe	 **16**	*E*-15% *Z*-8%
13	$MeNH_2$	 **17**	78%

intermediate **2**.[3] The other product was identified as an *E*/*Z* mixture of the semicarbazone **4** (Scheme 1). In an attempt to improve the selectivity in favor of the semicarbazone, an excess of amine (400−1500 mol %) was used. Although under these conditions the urea was still observed, the semicarbazone became the major product with yields ranging from 90 to 60% when alkylamines were used (Table 1). Interestingly, the excess of amine helped to prevent the formation of other byproducts like symmetrical ureas and *N*-carbamoyloxyureas, which are generated by degradation of the acyl nitroso intermediates.[8] This observation highlights the short half-life of the acyl nitroso species and the requirement for the rapid trapping of the nitroso group.

As shown in Table 1, the substitution of the starting *N*-hydroxyurea does not seem to be crucial for the feasibility of the reaction, although the steric hindrance and/or the electron effect of the amine appear to have a deleterious effect on the formation of the semicarbazone. Amines derived from alanine and valine led to the formation of the corresponding semicarbazones **15** and **16** in low yields (entries 11 and 12), while the ethyl ester of glycine afforded semicarbazone **14** in 62% yield (entry 10).[9] In several cases, the semicarbazones were obtained as a mixture of *E* and *Z* isomers. Indeed, a strong tendency for the *E*↔*Z* isomerization was found. When a single isomer could be isolated from the mixture, in most cases this evolved toward a new *E*/*Z* mixture, making characterization of these compounds difficult. Nevertheless, some amines, particularly benzylamines, afforded the corresponding semicarbazones as a single isomer (Table 2). In this regard, the observation of a sole isomer in the case of benzylamines might be an indication of a geometrical bias for the phenyl group. The *E*/*Z* geometry was determined when possible on the basis of the observed NOE effects and by comparison of ^1H and ^{13}C NMR chemical shifts. Analogous reactivity was found with *N*-hydroxythioureas, which afforded the corresponding thiosemicarbazones in good yields (Table 1, entry 13 and Table 2, entry 8).

To propose a mechanistic rationale for these results, it seemed to us that the reaction of an amine with a carbamoyl nitroso function could follow two different

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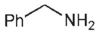
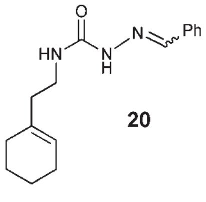
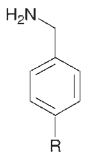
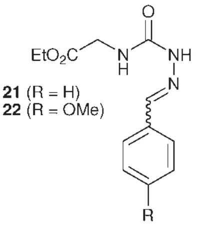
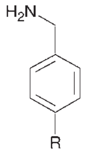
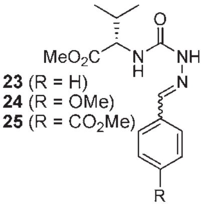
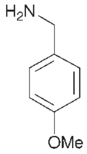
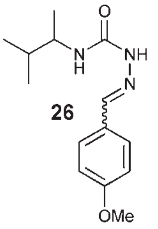
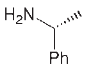
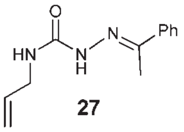
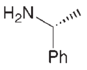
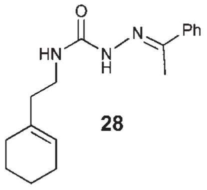
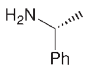
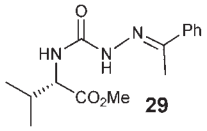
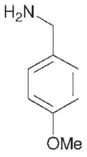
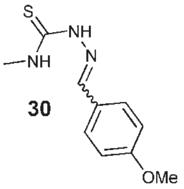
(8) The oxidation of *N*-hydroxyureas in the absence of amine afforded a 1:1 mixture of the corresponding symmetrical urea and *N*-carbamoyloxyurea (80% yield). See Supporting Information for details (compounds **38** and **39**).

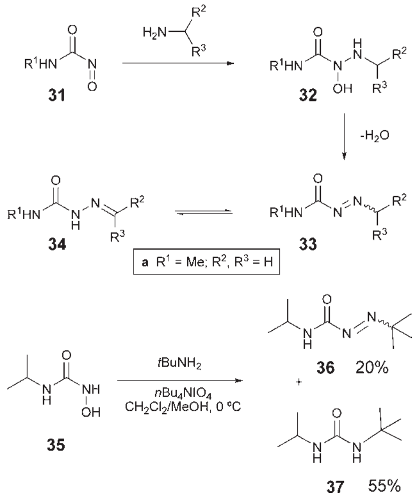
(9) Various hindered amines give rise to the urea as the only product under the same reaction conditions. See Supporting Information for details (compounds **18** and **19**).

Table 2. Semicarbazones from Benzylamines

entry	amine	semicarbazone	yield
1		 **20**	75%
2		 **21** (R = H) **22** (R = OMe)	62% (R = H) 71% (R = OMe)
3		 **23** (R = H) **24** (R = OMe) **25** (R = CO_2Me)	68% (R = H) 62% (R = OMe) 67% (R=CO_2Me)
4		 **26**	67%
5		 **27**	52%
6		 **28**	59%
7		 **29**	55%
8		 **30**	68%

pathways. The addition of the amine to the carbonyl group would lead to the formation of the urea, as expected,[3] while the addition of the amine to the nitroso group could explain the final formation of the semicarbazone. The condensation of aryl nitroso derivatives with arylamines to give azo compounds is known,[10] and this process proceeds in either acidic or basic media.[11] Likewise, trifluoronitrosomethane is known to react with alkylamines to yield trifluoromethylazoalkanes.[12] According to our hypothesis, the initial addition of the amine to the nitroso group would generate an azo intermediate that would evolve to give the final semicarbazone (Scheme 2). The presence of a product that disappears to afford the semicarbazone was detected in some cases by TLC. In the case of (*R*)-1-hydroxy-3-(1-phenylethyl)urea treated with isopropylamine, this product was isolated after flash chromatography (8% yield). In an attempt to characterize this compound, we observed that the transformation of this intermediate into the corresponding semicarbazone can be monitored by ^{1}H NMR (Figure 1). After 120 h at 25 °C in deuterated chloroform, the semicarbazone was the major product in a 99:1 ratio. The ^{1}H NMR spectrum of this short-lived compound was consistent with the structure of the postulated azo intermediate, which presumably isomerizes to give the final semicarbazone. This isomerization could take place since a proton exchange is possible in the α-position to the nitrogen of the amine. The use of an amine bearing a tertiary substituent would lead exclusively to the azo compound since the tautomerization is not feasible. With this purpose, *N*-hydroxyurea **35** was treated with *t*BuNH$_2$ in the presence of *n*Bu$_4$NIO$_4$. Besides urea **37** (55% yield), the expected acyl azo compound **36** was isolated in 20% yield (Scheme 2).

Scheme 2. Mechanistic Proposal



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(10) (a) Boyer, J. H. *In The Chemistry of the Nitro and Nitroso Groups*, Part 1; Feuer, H., Ed.; Interscience: New York, 1969; pp 278−283. (b) Davey, M. H.; Lee, V. Y.; Miller, R. D.; Marks, T. J. *J. Org. Chem.* **1999**, *64*, 4976.

(11) (a) Mills, C. *J. Chem. Soc.* **1895**, *67*, 925. (b) Campbell, N.; Henderson, A. W.; Taylor, D. *J. Chem. Soc.* **1953**, 1281.

(12) Abe, T.; Joo, Y.-H.; Tao, G.-H.; Teamley, B.; Shreeve, J. M. *Chem.—Eur. J.* **2009**, *15*, 4102.

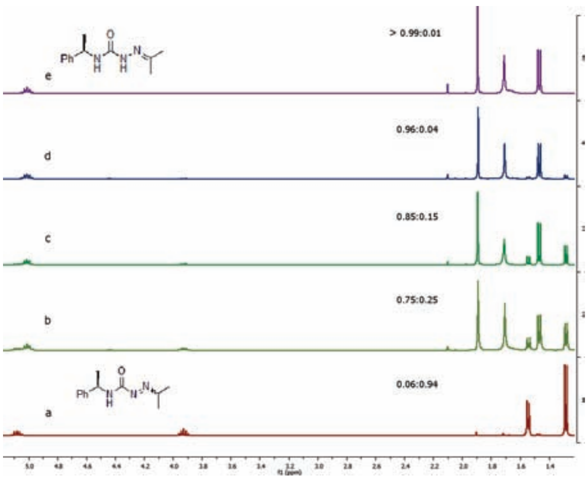

Figure 1. Azo-semicarbazone isomerization: (a) 0 h, (b) 24 h, (c) 36 h, (d) 48 h, and (e) 120 h.

All of these results seem to support a mechanism in which an azo compound **33** is initially formed by condensation of the amine with the nitroso group, presumably with the elimination of water. Further tautomerization leads to the final semicarbazone **34**.[13] This significant preference for the semicarbazone form prompted us to carry out calculations at the DFT level to gain some insights into the structural features that favor the semicarbazone over the initial acyl azo compound.

A conformational search for azo compound **33a** and semicarbazone **34a** (Scheme 2) showed that whereas the azo compound has two meaningful conformers, the semicarbazone only has a single conformer. In addition, the semicarbazone is at least 10 kcal mol^{-1} more stable than the azo compound. This finding is in full agreement with the aforementioned experimental results. Quantum theory of atoms in molecules (QTAIM) calculations were performed to ascertain the reason for this energy difference. Initially, delocalization indexes were calculated since it seemed that the semicarbazone might have higher electron delocalization than the azo compound. Although delocalization indexes correlate well with bond distances, no appreciable variation of delocalized electron population was found between the two tautomers. However, analysis of atomic energies $E(\Omega)$ showed small differences between tautomers in the atoms involved in tautomerization. Thus, the sum of the atomic energies of the atoms involved in the tautomerization is *ca.* 0.13 hartree lower in the semicarbazone.[14] This can be related to the differences in electron distribution associated with different electronegativity values for nitrogen and carbon. The ability of hydrogens to experience significant variations of electron population depending on their environment plays an important role in diverse chemical processes.[15] For example, electron density transference from hydrogens to more electronegative atoms is a general stabilization mechanism that can be found on the grounds of diverse tautomeric and conformational equilibria.[16]

In summary, we have described an unprecedented mode of reactivity of acyl nitroso compounds. The condensation of carbamoyl nitroso compounds, obtained by oxidation of *N*-hydroxyureas, with amines afforded semicarbazones. Although the substitution of the nitrosyl moiety might compete to afford the corresponding urea, an excess of amine led to semicarbazone as the major product, which is presumably formed through isomerization of an initially generated acyl azo compound. DFT calculations show that semicarbazones are more stable than the corresponding azo compounds because of electronegativity effects on changing a C−H bond to an N−H bond. Contrary to the expected situation, delocalization is not substantially affected on changing from one tautomer to the other.

Acknowledgment. We are grateful to the Xunta de Galicia and the Spanish Ministerio de Ciencia e Innovación. Helpful discussions with Prof. Ricardo A. Mosquera are gratefully acknowledged.

Supporting Information Available. Experimental information and data for all new compounds. Detailed calculations results and discussion, SCF and free energies, Cartesian coordinates, and delocalization indexes for compounds **33a** and **34a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] (a) For a precedent on the isomerization of a carbamoyl azo compound to the corresponding semicarbazone see: Horner, L.; Fernekess, H. *Chem. Ber*. **1961**, *94*, 712. (b) See also ref 12 for the isomerization of trifluoromethylazoalkanes to hydrazones.

[14] See Supporting Information for a detailed discussion of the calculation results.

[15] Stutchbury, N. C. J.; Cooper, D. L. *J. Chem. Phys.* **1983**, *79*, 4967.

[16] (a) González Moa, M. J.; Mandado, M.; Mosquera, R. A. *Chem. Phys. Lett.* **2006**, *428*, 255. (b) Vila, A.; Mosquera, R. A. *J. Comput. Chem.* **2007**, *28*, 1516.